PATENT ABSTRACTS OF JAPAN

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(54) **ERECTION DYSFUNCTION REMEDY**

(57)Abstract:
PROBLEM TO BE SOLVED: To obtain an erection dysfunction remedy having the activity to increase the level of cyclic guanosine monophosphate declined in production by NG-monomethyl-L-arginine or the like including symmetry-NG,N'G-dimethyl-L- arginine as effective ingredient.
SOLUTION: This remedy is obtained by including, as effective ingredient, symmetry-NG,N'G-dimethyl-L-arginine(SDMA) or a salt thereof (e.g. hydrochloride, acetate), optionally in combination with sildenafil citrate salt or the like. To prepare this remedy in the form of a solid oral preparation, a vehicle, binder, disintegrant, etc., are added. As for the method for administrating this remedy, it is administered pref. 30 min to one hour before desiring penis erection, its dose being appropriately 5-100 mg at a time orally; it is recommended that in the form of a patch, e.g. a tape containing SDMA (salt) at 1-50 mg/cm2 is used; and in the form of a liniment, e.g. an ointment, cream containing SDMA (salt) at 1-100 mg/g.

CLAIMS

[Claim(s)]
[Claim 1]An erection malfunction improving agent which makes an active principle symmetry N^G and N'^G-dimethyl- L-arginine or its salt.

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* NOTICES *

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention]This invention relates to the improving agent of phallus erection malfunction.
[0002]
[Description of the Prior Art]The male phallus erection insufficiency patient is said to increase rapidly with the increase in an elderly population. The increase in an arteries-of-the-penis blood flow, control of blood leaking from the vena bulbi penis, and relaxation of a spongy body organization are needed for erection. Now, the cures currently performed by the urology department are pharmacotherapy and a phallus prosthetic dentistry implement. As pharmacotherapy, although papaverine hydrochloride, injection into the spongy body of prostaglandin E_1, etc. are mentioned as a possibility, there is a problem in respect of validity, side effects, simple nature, etc., and it is hardly carried out.
[0003]On the other hand, manufacturing approval of the sildenafil citrate (sildenafil is called hereafter) was done by FDA recently as an erection malfunction treating agent which can be administered orally. An erection promotion operation of this sildenafil is due to a vascular smooth muscle extension operation of a phallus.
In details, more by the inhibitory action of the phosphodiesterase 5 (PDE-5) which is a dialytic ferment of a cyclic guanosine monophosphate (cGMP). It is a thing of making the cGMP concentration in the vascular smooth muscle cell of a phallus increase, reducing the intracellular Ca^{2+} concentration concerned by that cause, bringing about relaxation (vasodilatation) and increased vascular flow of a vascular smooth muscle, and making a phallus rise up as the result.

[0004]
[Problem to be solved by the invention]However, since there is no vascular selectivity to which the ratio of consumed water of sildenafil is only about 50%, and a blood flow is made to increase, side effects also pose a problem. Therefore, the purpose of this invention is to provide the new erection malfunction improving agent based on a new action mechanism.
[0005]
[Means for solving problem]Then, in the research way for this invention person to solve the causal relationship of the manifestation of erection malfunction, and the several-kinds biogenic substance among blood, It discovered that N^G-monomethyl L-arginine (L-NMMA) and asymmetry N^G and N^G-dimethyl- L-arginine (ADMA) concentration was increasing intentionally compared with a healthy person in the erection malfunction patient. On the other hand, these L-NMMA and ADMA, By a vascular endothelial cell, with a nitric-oxide-synthesis enzyme from L-arginine. The step at which nitric oxide is biosynthesized. The operation to check. It has (Journal of Cardiovascnlar Pharmacology and 1992;20:S60-S62, British Journal of Pharmacology, 1995; 115:1001-1004), It is also shown clearly that L-NMMA and ADMA are incorporated in endothelial cells in advance of the manifestation of this operation (American Journal of Physiology, 1995;C750-C756). Namely, the result in which the blood drug concentration of L-NMMA and ADMA rises in an erection malfunction patient, Since the nitric oxide biosynthesis ability within a phallus vascular endothelial cell falls and the fall of the cGMP biosynthesis from guanosine triphosphate (GTP), i.e., the vasodilatation of the corpus cavernosum penis, falls into a phallus

vascular smooth muscle cell, It was thought that the increase in the blood drug concentration of L-NMMA and ADMA made one of the main factors of erection malfunction.
[0006]The place where this invention person searched the substance which checks the membrane transport into a vascular endothelial cell for these L-NMMA or ADMA out of blood based on this viewpoint, There is an operation which makes the amount of cGMPs to which the generated amount fell [symmetry N^G and N'^G-dimethyl- L-arginine (SDMA) or its salt] by L-NMMA or ADMA also unexpectedly completely increase, It finds out that it is useful as an erection malfunction improving agent by the amount increasing action of cGMPs, and came to complete this invention.
[0007]That is, this invention provides the erection malfunction improving agent which makes SDMA or its salt an active principle.
[0008]
[Mode for carrying out the invention]SDMA used for this invention -- this very thing -- the operation which makes the amount of cGMPs to which the generated amount fell by L-NMMA and ADMA in arteries of the penis increase although it is a publicly known compound -- a relation with an erection function is not reported further at all.
[0009]According to this invention person's research, SDMA or its salt improves erection malfunction like the above by the operation which re-raises the fall of the cGMP production amount in the vascular smooth muscle cell of the phallus by L-NMMA and ADMA which are increasing specifically into an erection insufficiency patient's blood.
[0010]As a salt of SDMA used for this invention, organic acid salt, such as mineral acid salt, such as a hydrochloride and sulfate, and acetate, is mentioned.
[0011]The medicine of this invention should just contain SDMA or its salt as an active principle, and may use it together with the aforementioned sildenafil etc. in addition to SDMA. An additive agent required for the medicine of this invention in addition to SDMA or its salt can be blended, and it can be made various dosage forms.
[0012]In order to prepare solid oral pharmaceutical preparation, after adding a binding material, disintegrator, lubricant, colorant, corrigent, an odor-masking agent, etc. to SDMA or its salt an excipient and if needed, a tablet, a coated tablet, a granule, powder medicine, a capsule, etc. can be manufactured with a conventional method. In order to prepare the liquid preparation for taking orally, corrigent, a buffer, a stabilizing agent, an odor-masking agent, etc. can be added to SDMA or its salt, and oral administration liquids and solutions, syrups, elixirs, etc. can be manufactured with a conventional method. When preparing injections, a pH regulator, a buffer, a stabilizing agent, an isotonizing agent, local anesthetic, etc. can be added in SDMA or its salt, and hypodermic, intramuscular, and vein internal use injections can be manufactured with a conventional method. When preparing an ointment, a base, stabilizer, a wetting agent, a preservative, etc. by which normal use is carried out are blended with SDMA or its salt if needed, and it is mixed and pharmaceutical-preparation-ized by a conventional method. What is necessary is just to apply said ointment, cream, gel, a paste, etc. to the usual base material with a conventional method, when manufacturing patches.
[0013]It is preferred to prescribe a medicine for the patient as a medication method of this invention medicine [which asks for erection of a phallus / 30 minutes - 1 hour] ago, and, in the case of taking orally, 5-100 mg per time is suitable as a dose. What is necessary is just to use [in the case of patches] 1 - 100 mg/g content ointment, cream, etc. using 1-50 mg / cm^2 content tape in spreading.
[0014]
[Working example]Next, although an embodiment is given and this invention is explained still in detail, this invention is not restricted to this at all.
[0015]L-NMMA in blood and ADMA concentration of a reference example 1 healthy adult man (ten persons) and an erection insufficiency patient (14 persons) were measured. L-NMMA in plasma and ADMA were quantified based on a publicly known method. That is, to plasma separated in accordance with a conventional method, trichloroacetic acid is added so that the last concentration may be 5%, and it centrifuges for 10 minutes by 1300xg to it. Under [a fixed

quantity / ADMA / L-NMMA and / high performance chromatography separates supernatant liquid 100 obtained microliter and].

[0016]

[Table 1]

グループ（1）健常成人男子

症例番号	年　齢	L-NMMA(pmo ℓ／mℓ)	ADMA(pmo ℓ／mℓ)
1	41	0	290
2	39	0	414
3	31	0	363
4	25	0	356
5	36	4	312
6	26	0	223
7	24	0	223
8	23	0	181
9	24	0	272
10	24	0	214
平均±S.E.		0.4±0.4	284.8±24.1

グループ（2）インポテンス患者

症例番号	年　齢	L-NMMA(pmo ℓ／mℓ)	ADMA(pmo ℓ／mℓ)
1	27	40	337
2	66	67	443
3	41	71	616
4	61	71	404
5	68	34	365
6	78	62	513
7	56	49	292
8	27	27	285
9	65	49	380
10	64	51	499
11	68	67	499
12	39	70	497
13	35	58	383
14	73	42	396
平均±S.E.		54.1±3.9 (p<0.005)	422.1±25.1 (p<0.005)

[0017]As a result, as shown in Table 1, in an erection malfunction patient group, it became clear that blood drug concentration of L-NMMA and ADMA was intentionally ($p < 0.005$) and high compared with a healthy person.

[0018]The cGMP production in embodiment 1 acetylcholine and the arterial smooth muscle cell by noradrenalin stimulus was also measured based on the publicly known method. That is, the carotid artery of the rabbit was extracted and the strip with a wet weight of about 5 mg which preserved endothelial cells was produced. 37 ** pre incubated for 20 minutes in Krebs liquid. Then, 3×10^{-6}M acetylcholine was added 15 minutes after 10^{-6}M noradrenalin addition, and it incubated for 15 more minutes. After ending reaction, promptly, the carotid artery strip was moved in 5% trichloroacetic acid, and it froze with liquid nitrogen. In accordance with the conventional method, cGMP was extracted during the organization, and it quantified using the commercial cGMP assay kit.

[0019]As a result, as shown in drawing 1, the cGMP production by stimulus of the acetylcholine and the noradrenalin in a vascular smooth muscle cell was clearly controlled by addition of L-NMMA. And it became clear that this cGMP production depressant action was intentionally recovered by SDMA.

[0020]The next experiment was conducted in order to explain a L-NMMA blood-drug-concentration rise of the erection malfunction patient who got by the embodiment 2 reference example 1, and the mechanism of the cGMP increasing action of SDMA obtained in Embodiment 1. The periphery was covered with dental resin, the rabbit thorax aortal preparation which exposed only endothelial cells was produced, and it incubated for 2 minutes at 10microM[^{3}H]-L-

NMMA (0.537 microcurie/(ml)) and 37 **. Endothelial cells incorporate [^{3}H]-L-NMMA selectively by this processing. 100microM SDMA controlled this incorporation nearly thoroughly so that clearly from drawing 2. Therefore, it became clear that SDMA inhibited powerfully the L-NMMA incorporation operation by an arterial hide cell.
[0021]2000 mg/kg internal use of the embodiment 3SDMA was carried out at ten mice, and general status and the existence of death were observed over one week. As a result, transition of weight and any change to a motor activity were not seen, either, but there was also no example of death. In ******** of main organs and an organization, there was no change considered to originate in medication. Therefore, it was presumed that the acute toxicity in internal use of SDMA exceeded 2000 mg/kg, and it was checked that safety is high.
[0022]
[Effect of the Invention]In this invention, the cGMP concentration in a vascular smooth muscle cell of the phallus which is falling is raised in an erection malfunction patient based on overincorporation of L-NMMA and ADMA.
Therefore, erection malfunction is improvable.

[Translation done.]

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DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]
[Drawing 1]It is a figure showing the recovery effect of SDMA to this with the cGMP density lowering operation by L-NMMA in an artery.
[Drawing 2]It is a figure showing the incorporation inhibition effect of SDMA to this with incorporation of L-NMMA to a vascular endothelial cell.

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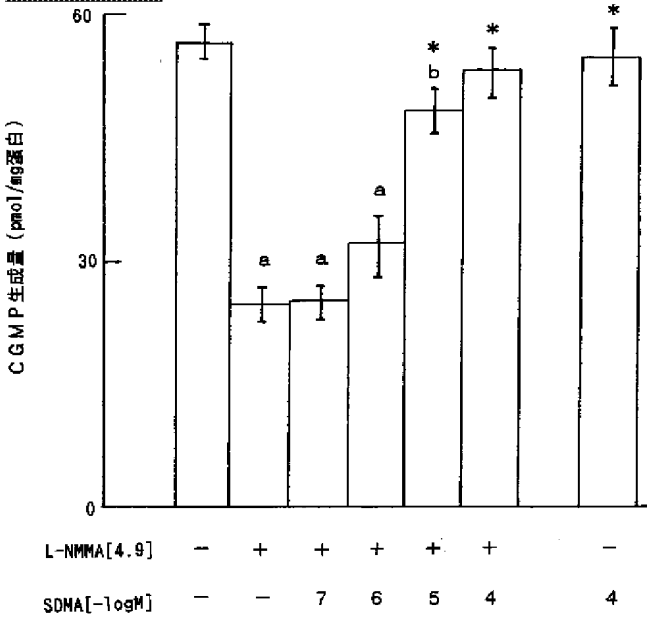
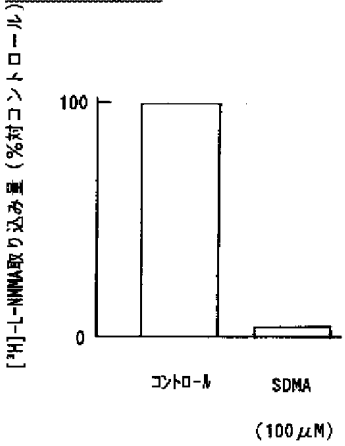
DRAWINGS

[Drawing 1]



a：p<0.005(対 L-NMMAなし)
b：p<0.05（対 L-NMMAなし）
＊：p<0.005(対 L-NMMA単独)

[Drawing 2]



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